Did Edward V suffer from histiocytosis X?

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Introduction

On the death of Edward IV on 9 April 1483, the 12-year-old Edward, Prince of Wales, left Ludlow where he had spent much of his childhood, to be proclaimed King in London. He reached the capital at the beginning of May, accompanied not by his own familiar Household officers with whom he had set out but by his paternal uncle and guardian, Richard of Gloucester. Initially lodged in the Palace of the Bishop of London, he was surrounded by his own small court, but still separated from his mother, brother and five sisters, while preparations continued for his coronation planned for 24 June. In mid-May, he transferred into the Royal Apartments at the Tower, a quite reasonable move since the traditional coronation procedure commenced with a ceremonial procession from the Tower to Westminster. His mother was eventually persuaded to release the nearly 10-year-old Prince Richard from sanctuary in the Abbot's house in Westminster, even though (according to Sir Thomas More) he was still recovering from sickness, so that he might join his elder brother, who lacked a playfellow, 'for their both disporte and recreacion'[1] (p 34, II). The brothers were re-united in mid-June at the Tower, after which time they were seen shooting and playing in the garden there. However, after the execution of Hastings, the King and his brother

> were withdrawn into the inner apartments of the Tower proper, and day by day began to be seen more rarely behind the bars and windows, till at length they ceased to appear altogether[2].

The rumours and contested succession that ensued have been followed by continued controversy amongst historians as to the reliability of contemporary accounts (particularly that by More, written some 30 years later), the manner of the presumed death of the princes in the Tower, and the degree of responsibility and involvement of Richard of Gloucester, Lord Protector, who had by then declared himself King. The dispute over the guilt of the latter shows little sign of ending.

Support for More's account of the princes' bodies being placed in a wooden chest and buried under a great heap of stones was strengthened by the discovery, in July 1674, of the skeletons of two children under the bottom stair of an external staircase that was being demolished in the White Tower. The workmen had initially thrown away the rubbish and some of the bones, being unaware of their possible import, but a number were recovered, although some had been damaged as a result of the labourers' earlier violence. Sir Christopher Wren was subsequently commanded to

> provide a white Marble Coffin for the supposed bodyes of ye two Princes lately found in ye Tower of London

The bones were duly deposited in the resultant marble urn and this placed in Henry VII's Chapel in Westminster Abbey, in 1678.

The bones remained undisturbed until 1933 when permission was granted by the Dean and Chapter of Westminster for their examination in the light of modern medical science, in order to confirm that they really were of human rather than animal origin, and if so, whether they belonged to two boys of about the reputed ages of the princes. The examination was conducted within Henry VII's Chapel by Lawrence Tanner, Keeper of the Muniments, and William Wright, professor of anatomy, with assistance from the orthodontist George Northcroft; the findings were then presented to the Society of Antiquaries before being published with photographs of the crania, mandibles and some of the other surviving long bones, together with radiographs of part of the jaws of both juveniles[3]. Relying heavily on the degree of dental development, Tanner and Wright were sufficiently convinced that these were the bones of two children of the reputed ages of the princes, and that there was nothing from the scientific point of view against their identification as such.

Subsequent biographers of Richard III have submitted these findings to other medical examiners, whose reports have generally (though not entirely unanimously) been in agreement in terms of the approximate ages of the incomplete skeletons. They have, however, stressed the weakness of the arguments concerning sex and consanguinity, and the suggestion that the reddish-brown stain on the skull of the elder child had arisen from his supposed suffocation. It must be emphasized that there have been no subsequent exhumations, with the result that present-day sophisticated biochemical testing and forensic investigative techniques have not been applied to the original material. All medical commentaries have therefore been based solely on the information provided by Tanner and Wright. One recent anthropometric reappraisal, however, has adduced the presence of Wormian bones in similar positions in the lambdoid sutures of both skulls as being strongly suggestive of relationship[4].

We are prepared to accept the probability that the skeletons are those of the two princes. We do not seek to challenge these views, but wish rather to concentrate on an aspect of oral pathology in the mandible of the elder juvenile that has been noted but variously diagnosed. As the conclusions of medical

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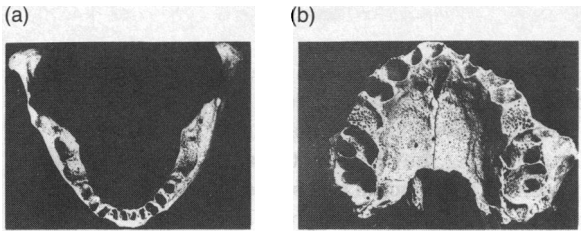

Figure 1. The mandible (a) and the maxilla (b) of the elder juvenile

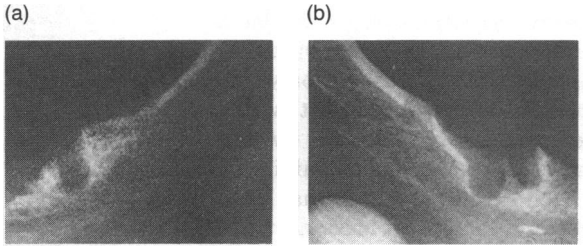

Figure 2. Radiograph of the mandible of the elder juvenile: (a) left molar region; (b) the right molar region

science seldom remain static, it may now be possible to explore further these observed pathological findings, and attempt to relate them to contemporary accounts of the health and behaviour of the young Edward V.

The mandible of the elder juvenile

At the exhumation, the mandible was in two pieces but was otherwise generally well preserved, possibly as a result of this skeleton having lain underneath that of the younger one, and hence having been less damaged by the workmen's excavations. All the teeth had been lost post-mortem, but the upper second premolars appeared to have been congenitally absent.

Working from plates produced from the original photographic negatives, the socket margins of the anterior two-thirds of the lower arch (from right to left second premolars) were noted as being still very crisply defined, as also were all those in the upper arch (Figure 1). In the region of the sockets of the lower left molars, there was an oval-shaped, well-demarcated lesion within the bone, which had a scooped-out but generally smooth appearance. The interdental septum between the molars had been destroyed as also had most of the inter-radicular septa. In the lower right molar region there was a similar although less well-developed lesion. Despite the absence of the original radiographs, their reproduction in *Archaeologia*[3] confirmed the clinical appearance and extent of the bone lesions. In addition, they showed no evidence of associated sequestra or sclerosis (Figure 2). There was no suggestion of any development of the lower third molars.

Previous discussion of the mandibular pathology

The bony lesions in the mandible have previously been variously described and diagnosed, but by anatomists and orthodontists rather than by forensic odontologists or oral pathologists. Since the concentration of interest has formerly been with the degree of dental development in order to age the skeleton, this emphasis is not entirely surprising, but may explain the divergent views and inferences.

In the original report, Tanner and Wright referred to 'extensive disease' affecting almost equally both sides of the lower jaw, originating in or around the molar teeth, but having spread on the left to cause destruction of the interdental septum between the first and second molars. They offered no diagnosis or cause for this, but suggested that it was of a chronic nature that could not have failed to affect general health. The gums would have been inflamed, swollen and septic, and doubtless associated with discomfort and irritability. Northcroft himself, in an address given subsequently to a dental audience, stated:

> these sockets were saucer shaped, pointing to prolonged sepsis following caries; no sign of true paradontal disease could be observed[5].

Non-clinical historians have subsequently remarked upon the bony pathology, but have referred sweepingly to 'gum disease' or 'toothache'[6], although sometimes including a footnote where they have sought the views of a dental commentator. One such, Lind, was very careful, however, not to offer any precise diagnosis for the biographer Elizabeth Jenkins. He confined himself to stating that loss of the interdental septa may arise from the spread of a periapical abscess from an adjoining tooth, or chronic gingival infection, where damaged gums allow the invasion of bacteria into bony areas[7]. More extensive commentary has been included by Audrey Williamson in her defence of Richard III, where views generally favour an infective aetiology, with references to rarefying osteitis, osteomyelitis and 'serious jaw disease'[8]. Morgan had pointed out that the diagnosis of chronic disease affecting the lower jaw and teeth might be 'possibly valid', that the observed bony changes might equally have been attributable to the result of decomposition. Lyne-Pirkis (an anatomist), on the other hand, was strongly in favour of osteomyelitis, which the victim might or might not have survived.

An alternative diagnosis

The original photograph indicates a relatively good state of preservation of the mandible (Figure 1), despite the loss of the teeth; it is unlikely, therefore, that post-mortem changes alone would account for the bone loss in the molar regions. Periodontal disease would almost certainly not be so localized, and most juvenile forms would involve the incisor teeth in addition to the molars. The overall pattern of bone loss, together with the absence of any associated sequestra or sclerosis on the radiographs, makes a diagnosis of osteomyelitis equally unlikely; furthermore, the surface appearance of the bony lesion is altogether too punched out and smooth for a progressive infective process. The appearances are, however, not dissimilar to those seen in histiocytosis X. Comparison with a radiograph of a jaw lesion from a 3-year-old boy (Figure 3) with histologically-confirmed histiocytosis X (eosinophilic granuloma) shows a similar, and typical, pattern of bone loss, even though in a much younger child. The multiple radiolucent areas involving the interdental and interradicular bone give the teeth an appearance of 'floating in air'[9].

Histiocytosis X comprises a group of disorders with diverse clinical manifestations but similar histological appearances with infiltration of the tissues by masses of proliferating histiocytes admixed with variable numbers of eosinophils. Although the aetiology is still not fully understood, the condition is usually divided clinically into one of three main forms which may

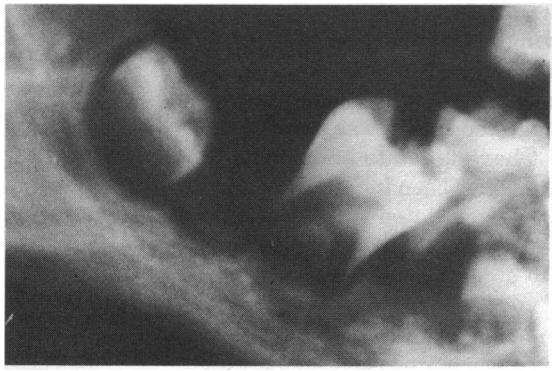

Figure 3. Radiograph of the right molar region of a 3-year-old boy with a confirmed diagnosis of eosinophilic granuloma

represent a spectrum of disease severity as opposed to separate entities. These are: (i) eosinophilic granuloma of bone, which can be either unifocal or multifocal; (ii) Hand-Schüller-Christian (HSC) disease (chronic disseminated histiocytosis X); or (iii) Letterer-Siwe disease (acute disseminated histiocytosis X). All, bar the latter which occurs predominantly in infants and is often rapidly fatal, typically begin in childhood or early adolescence, particularly in males. HSC disease is usually slowly progressive, classically presenting with a triad of osteolytic skull lesions, diabetes insipidus and exophthalmos. In contrast, eosinophilic granuloma is usually restricted to bony sites, in particular ribs, pelvis, skull, facial and long bones. The lesions often develop quickly and may cause a dull, constant pain presenting in the jaws with swelling, a soft tissue mass and loosening of the teeth in the affected areas (usually the molar regions)[10].

The prognosis for histiocytosis X is now good, although one of the most significant factors influencing morbidity and mortality is the extent of the disease at the time of initial diagnosis and the number of organ systems involved. Onset in the younger patient is usually associated with progressive and rampant disease, whereas in the older patient, it tends to be more localized. Both HSC disease and eosinophilic granuloma are now usually managed with either radiotherapy, surgery or chemotherapy and have an excellent prognosis, but in their absence the disease, unless it burns itself out, can be a progressively destructive condition which may prove fatal. This may, however, take many years, with periods of remission interspersed with variable progression, depending on the extent of systemic involvement.

Although the bony changes in the mandible under investigation are consistent with those that may be observed in histiocytosis X, and more specifically in eosinophilic granuloma, the disease cannot be confirmed conclusively in the absence of soft tissue histological examination. Nevertheless, its known prevalence in pre-puberty males would seem to offer some support to the likelihood of the bones being those of a boy. This, in its turn, might therefore offer a little further support to the arguments that this skeleton was indeed that of the young Edward V.

Behaviour and health of Edward V

If the possibilities are accepted that the skeleton of the elder juvenile was that of Edward V and also that he was suffering from a form of histiocytosis X, the question may then be raised as to how far present-day knowledge of the clinical pattern of this condition correlates with contemporary accounts of the prince's health and behaviour.

The young Edward's own Household had been established at Ludlow when he was 3 years old, for a safe up-bringing. The day was tightly regulated for the training of the future king, but he was to have continually in his household a physician and surgeon 'sufficiente and cunninge'[11]. In an age of high infant mortality, the boy's health and well-being were of paramount importance. According to a miniature of *c.* 1477, he seems to have inherited not only his mother's golden hair but also her facial beauty, although not her heavy, drooping eyelids. Whilst it may have been politic to praise the Prince of Wales, it would nevertheless seem that he was not only tall, slender and attractive but highly intelligent, with a considerable degree of personal charm. By the time of his father's death, the academic training of a gifted pupil had been excellent, as also had been the psychological preparation from his maternal uncle Anthony Lord Rivers.

Although a 12-year-old boy in the Middle Ages, trained from the outset as a future king, cannot be regarded as a child, the events of April 1483 must nevertheless have been taxing. The news of his father's death, the altered behaviour of everyone approaching him after his accession, then 5 days' travelling from Ludlow only to be faced with his virtually unknown uncle Gloucester, in black, instead of his familiar uncle Rivers, would have made huge demands on his inner resources. His confidence in his mother's family must have been shaken by Gloucester's claims that Rivers and others were conspiring to deprive him of the office of Protector. When his trusted chamberlain and elder half-brother were arrested before his eyes, it is little wonder that the presence of none but alien attendants about him finally breached his self-control.

Once in London, the continued separation from his mother and siblings must have been both emotionally and intellectually disturbing. He would have been acutely aware of the inherent dangers of minority rule and the likelihood of political power struggles, even if, initially, he had been in no fear for his life. There was some relief when his younger brother Richard was released from sanctuary, to join him at the Tower. However, Jean Molinet's description that

> the eldest was simple and very melancholy, but the youngest was joyous and witty, nimble and ever ready for dances and games

need not have stemmed from romantic embroidery of rumour[12].

Amongst the continental visitors to London at this time was an Italian named Domenico Mancini. However, it was not until 1936 that a manuscript was published of his account of Richard of Gloucester's seizure of the throne. Its importance lies in the fact that Mancini was unlikely to have been amongst the ranks of the later Tudor propagandists setting out to blacken Richard's name, but was writing of events seen or currently being discussed. He has been criticized for his sometimes cavalier disregard of chronology and general reluctance to disclose his sources of information, but he would certainly seem to have enjoyed direct access to the court during the last period of Edward IV's reign. There is one Englishman specifically named by Mancini, however,

who appears to have had quite strong connections with the court for many years, and who may therefore have been the one most likely to have provided confidential information. This was the physician John Argentine (1443-1508), who was not only in attendance on Edward V but was later to become physician to Henry VII's baby son Arthur in 1486, and eventually provost of King's College, Cambridge.

According to Mancini, who had departed from London just prior to Richard's coronation in early July 1483[2]:

> But after Hastings was removed, all the attendants who had waited upon the king were debarred access to him. . . . The physician Argentine, the last of his attendants whose services the king enjoyed, reported that the young king, like a victim prepared for sacrifice, sought remission of his sins by daily confession and penance, because he believed that death was facing him.

Sir Thomas More, who could never have seen Mancini's account, supports the depression of the young king in his later reconstruction[1] (p 85, II)

> After which time the prince neuer tyed his pointes, nor ought rought of hymselfe, but with that young babe hys brother, lingered in thought and heauines til this tratorous death, deliuered them of that wretchednes.

There is no reference in either account, and particularly in the former (which was probably derived from Argentine himself), to Edward being ill. The late presence of the physician in itself is not confirmatory of a health problem. Indeed, an important prisoner was frequently permitted both priest and physician so that the captors could argue that both spiritual and temporal needs were being ministered unto. The time-scale is too short for the privations of incarceration to have produced a deficiency disease such as scurvy, which might have produced oral pathology, although Molleson has recently put forward a suggestion that the princes' deaths may have occurred in 1484 rather than in the late summer of 1483, as some historians have argued[13]. Scorbutic effects would, in any case, have been more generalized.

If the young King had merely had toothache, the surgeon or his father's former barber could have dressed or extracted it without undue difficulty, despite the absence of modern anaesthesia. It is quite feasible that the surgeon did, in fact, remove the lower left first molar as a result of denudation of bony support, or because of local discomfort arising from secondary infection. The general malaise that may accompany a multifocal form of histiocytosis X could well have contributed to the boy's lowness of spirits, but cannot be held as solely responsible; the non-clinical historians' sympathies about 'toothache' and 'gum disease' may reflect more their own personal experiences.

It has already been noted that the prognosis for histiocytosis X is now good, although still dependent on the extent of the disease at the time of the initial diagnosis and the age of the individual. The extent of the disease in the presumed Edward is, of necessity, unknown. However, Tanner and Wright made no reference to any bony lesions in the other surviving bones, and it is now recognized that subjects with involvement of one or more bones and an absence of visceral lesions almost never die of the disease[13]. It may, therefore, be cautiously opined that the primary cause of death of the young Edward was not his disease alone, as some non-clinical historians have suggested in their attempts to exonerate Richard, although it may have weakened his resistance to other stresses.

Nevertheless, it cannot be ignored that the subsequent pretenders to the throne claimed to be not Edward but his younger brother Richard, Duke of York, or Edward, Earl of Warwick (son of the Duke of Clarence). There may have been some awareness that the young king was not as well as he might have been, but that this was submerged in the subsequent rumours and revulsion that swept London and then Europe. Minority rule always generated uncertainties and machinations, but the murder of children was abhorrent. There must always remain the possibility, though, that even if Edward had been crowned, he might not have survived beyond 5 years. Even had an expedient marriage produced an heir other than his younger brother, the problems of minority rule would have remained and the Yorkist-Lancastrian feud could have persisted still longer.

Conclusions

The bony pathological changes observed in the mandible of the presumed elder of the princes in the Tower are consistent with those that may be observed in histiocytosis X, and more specifically in multifocal eosinophilic granuloma. Whilst this does not conclusively confirm the identify of the skeleton as the uncrowned Edward V, the prevalence of the disease in pre-puberty males would add some further support to the likelihood of this presumption. The observed extent of the disease would suggest that it was not the most likely primary cause of death.

Acknowledgments: Figure 1 (a) and (b) are reproduced by courtesy of the Dean and Chapter of Westminster. Grateful thanks are extended to the Department of History, the University of Newcastle-upon-Tyne, for assistance towards the two plates from the original negatives of the exhumation.

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